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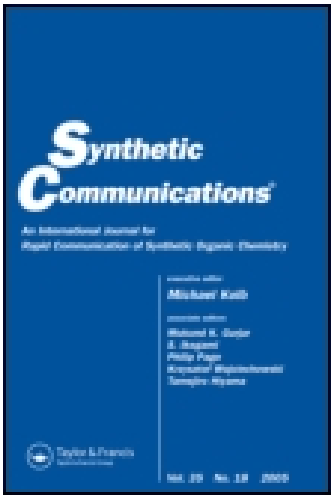

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Use of R-Pantolactone in the Synthesis of L-Tert Leucine Derivatives

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USE OF R-PANTOLACTONE IN THE SYNTHESIS OF L-*TERT* LEUCINE DERIVATIVES

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Abstract : *A 4 step synthesis of the N-Boc-ß,ß-Dimethyl Homoserine lactone from inexpensive, commercially available R- Pantolactone is described.*

In the hope of achieving enhanced proteolytic stability and superior biological activity, we have been exploring the synthesis of novel α–amino acids and their derivatives for incorporation into peptidomimetic enzyme inhibitors. Of particular interest to us was rapid synthetic access to various γ substituted *tert*-leucine derivatives. Recently several new approaches to *tert*-leucine derivatives have been reported.[1] Our route utilizes R-pantolactone as the chiral precursor. While pantolactone itself has been used as a chiral auxiliary in asymmetric rhodium catalyzed cyclopropanations[2], to our knowledge it has not been used to prepare L *tert*-leucine derivatives. L-*tert*-leucine has previously been converted to various derivatives which induce asymmetric transformations.[3] Both oxazolidinone **1** and oxazoline **2** are chiral auxiliaries derived from L-t*ert*- leucinol.[4,5] One drawback to use of these auxillaries is the relative expense of L-*tert*-leucine compared to that of the naturally occurring amino acids.

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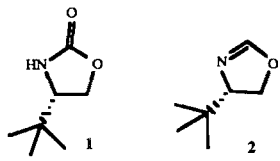

Herein a 4 step route to a protected *tert*-leucine derivative; N-Boc-β,β-Dimethyl Homoserine lactone **3a** from commercially available R-pantolactone **4** is reported (Scheme 1). This lactone would be a convenient starting material for the preparation of novel chiral oxazolidinones and oxazolines that may be useful chiral auxillaries. Reaction of **4** with 1.1 eq. triflic anhydride and 1.25 eq. pyridine in CH_2Cl_2 at -78 ^{0}C afforded the crystalline triflate **5** in 92% yield. Attempts to displace the triflate with sodium azide in DMF at elevated temperatures resulted in extensive decomposition of starting material and the formation of numerous side products, while use of lithium azide in acetonitrile was clean the rate was quite slow (~40 % conversion after 24 hours). Fortunately, when **5** was reacted with 1.0 eq. tetrabutyl ammonium azide[6] in $CHCl_3$ or toluene, smooth conversion to **6** occurred. Typically after 4-6 hours the reaction is complete and the crystalline azide **6** was isolated in 87% yield. It is noteworthy that **6** possesses the same absolute configuration of natural L-α-amino acids. Catalytic hydrogenation of **6** in the presence of 1.0 eq. of p-toluenesulfonic acid afforded a quantitative yield of the amino tosylate **7**. Coupling of **7** with various N-protected amino acids under standard coupling conditions (EDC / HOBt) yielded the expected dipeptide products. Alternatively, reaction with either $(Boc)_2O$ or Cbz-Cl gave the N-protected amino lactones **3a** and **3b** respectively. The overall yield from **4** to **3a** is 60-65 % and all of the reactions are amenable to multigram scale. The chiral purity of **3a** was determined by conversion to the Mosher's amide via deprotection with 4N HCl and reaction with (S)- Mosher's acid chloride.[7] Examination of the ^{19}F-NMR (3OOMHz, $CDCl_3$) showed a singlet at -69.48 ppm. Similarly the Mosher's amide prepared from (S)- Mosher's acid chloride and the amino tosylate derived from racemic pantolactone via the above sequence showed 2 singlets of equal intensity at -69.05 and -69.48 ppm.

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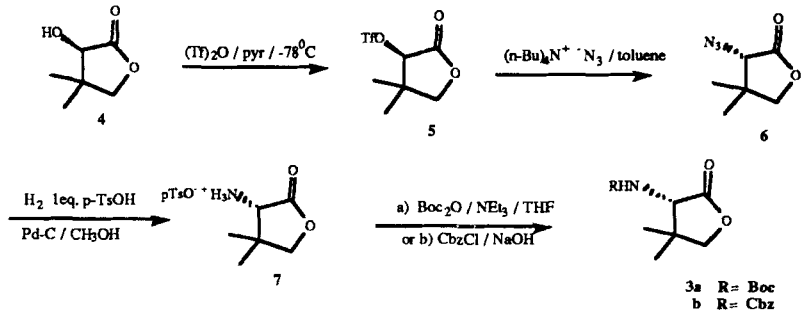
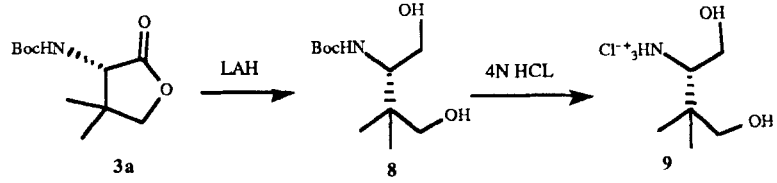


Scheme 1

Reaction of **3a** with potassium hydroxide in water - dioxane followed by lyophilization and treatment with diphenyl bromomethane in DMF[8] gave 60% of the hydroxy ester along with starting lactone (similar results were obtained with a one pot procedure using potassium trimethylsilanoate, 18-Crown-6, diphenylbromomethane in THF).[9] Swern oxidation[10] of the crude reaction followed by flash chromatography yielded the pure aldehyde (~60 % from **3a**).[11] Unfortunately we were unable to prove the chiral purity of the aldehyde due to the presence of rotomers. Alternatively, reaction of **3a** with LAH in diethyl ether gave, after chromatography, 60% of the crystalline N-Boc amino diol **8**. Deprotection of **8** with 4N HCL in dioxane gave the corresponding amine hydrochloride **9** as a clear oil. (Scheme 2). The chiral dihydroxy amine hydrochloride **9** can be transformed to a variety of chiral compounds. We hope to report on the incorperation of these compounds into biologically active molecules in the future.



Scheme 2

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EXPERIMENTAL

GENERAL

Melting points were obtained on a Thomas-Hoover capilliary device and are uncorrected. Optical rotations were obtained on an Autopol 3 automatic polarimeter. 1H-NMR and 19F-NMR were recorded at 300 MHz or 400 MHz on Varian VXR 300 or VXR 400. All reagents and dry solvents were obtained from Aldrich Chemical Co. with the exception of lithium azide which was bought from Eastman Kodak.

PREPARATION OF 5

A 250 ml round bottom flask equipped with magnetic stir bar, N_2 inlet, and addition funnel was charged with 12.0 g (92 mmol) R-Pantolactone, 9.2 ml (116 mmol) pyridine in 125 ml CH_2Cl_2. The reaction was cooled to -78^0 C and 28.6 g (101 mmol) triflic anhydride was added dropwise. The reaction was stirred 20 minutes at -78^{0}C then 1 hour at RT. The reaction mixture was concd. in vacuo and partioned between Et_2O and 5% aqueous potassium hydrogen sulfate. The combined organics were washed with saturated sodium bicarbonate, brine, dried over sodium sulfate, and concd. in vacuo to 22 g triflate **5**. mp 33-34 ^{0}C. $[\alpha]_D$ = +11.5^0 (c=10, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$): δ 5.1 (s, 1H), 4.15 (q, 2H), 1.28 (s, 3H), 1.2 (s, 3H). HRMS (FAB) cacld. for $C_7H_9O_5SF_3$ [M+Li]: 269.0283, Found 269.0285.

PREPARATION OF 6

A 100 ml round bottom flask equipped with magnetic stir bar and N_2 inlet was charged with 1.95 g (7.4mmol) **5**, 2.2g (7.5 mmol) tetrabutylammonium azide in 40 ml dry toluene.[12] After 4 hours the reaction was concd. to 1/2 volume and poured into water and extracted with Et_2O. The organic phase was washed with saturated sodium bicarbonate, 5% aqueous citric acid, and brine. The organic phase was dried and concd. *in vacuo* to 1.0 g (87 %) of azide **6**. mp 66-68 ^{0}C. $[\alpha]_D$ = -150.2^0 (c=1, $CHCl_3$). ^{1}H-NMR (300MHz, $CDCl_3$): δ 4.0 (q, 2H), 3.9 (s, 1H), 1.4 (s, 3H), 1.2 (s, 3H). HRMS calcd. for $C_6H_9N_3O_2$: 155.0695, Found 155.0713.

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PREPARATION OF 7

A 100ml Fisher Porter vessel was charged with 1.95 g (12.6 mmol) of **6**, 2.40 g (12.6 mmol) p-toulenesulfonic acid, a catalytic amount of 10% Pd-C in 40 ml MeOH. The mixture was hydrogenated for 1 hour, filtered thru Celite, and concd. *in vacuo* to 3.75g (94%) **7**. mp 213-215 ^{0}C. $[\alpha]_D$ = +6.0^0 (c=.5, MeOH). 1H-NMR (300MHz, $DMSOd_6$): δ 8.7 (br s, 3H), 7.45 (d, 2H), 7.1 (d, 2H), 4.25 (s, 1H), 4.15 (q, 2H), 2.3 (s, 3H), 1.25 (s, 3H), 1.0 (s, 3H).

PREPARATION OF 3a

A 100 ml round bottom flask equipped with magnetic stir bar and N_2 inlet was charged with 2.5g (.78 mmol) **7**, 1.74 g (.78 mmol) $(Boc)_2O$, 2.2 ml (15.7 mmol) NEt_3 in 40 ml dry THF. After overnight stirring at RT the reaction mixture was concd. in vacuo and partioned between EA and saturated sodium bicarbonate. The combined organics were washed with 5% aquoeus potassium hydrogen sulfate, brine, dried over sodium sulfate, and concd. *in vacuo* to 1.78 g white solid **3a**. A analytical sample was obtained by flash chromatography (30% EA-H) on silica gel. mp 138-140 ^{0}C. $[\alpha]_D$ = +63^0 (c=1, $CHCl_3$). 1H-NMR (300MHz, $CDCl_3$): δ 4.8 (br s, 1H), 4.4 (d, 1H), 4.0 (q, 2H), 1.5 (s, 9H), 1.25 (s, 3H), 1.0 (s, 3H). HRMS (FAB) calcd. for $C_{11}H_{19}NO_4$ [M+Li]: 236.1474, Found 236.1528.

PREPARATION OF 8

A 100 ml roumd bottom flask equipped with magnetic stir bar, N_2 inlet, reflux condenser, and addition funnel was charged with 5.4 ml of 1M LAH in Et_2O and 5 ml dry Et_2O. The solution was heated to reflux while 815 mg (3.6 mmol) of **3a** in 5 ml Et_2O and 5 ml THF were added dropwise. The reaction was refluxed 2 hours then stirred at RT overnight. The reaction was quenched by addition of 5ml of brine and 5ml of 5 % aqueous sodium hydroxide. After extraction with EA and concentration *in vacuo* the product was purified by flash chromatography to yield 470 mg (58 %) of diol **8**.[13] mp 105-107 ^{0}C. $[\alpha]_D$ = -8.5 ^{0} (c=8, $CHCl_3$). 1H-NMR (300MHz, $CDCl_3$): δ 5.15 (br s, 1H), 3.75 (dq, 2H), 3.6 (m, 1H), 3.4 (d, 1H), 3.2 (d, 1H), 2.9 (br, 2H (O-H)), 1.45 (s, 9H), 1.0 (s, 3H), 0.85 (s, 3H). HRMS calcd. for $C_{11}H_{23}NO_4$ (M+H) : calcd. 234.1705, obs.. 2341729.

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PREPARATION OF 9

A 100 ml round bottom flask equipped with magnetic stir bar and N_2 inlet was charged with 375 mg **8** in 10 ml 4N HCl in dioxane. After stirring 20 minutes at RT the reaction mixture was concd. *in vacuo* to 280 mg (94 %) clear syrup. $[\alpha]_D$ = + 25.4 ^{0} (c=2.4, MeOH). ^{1}H-NMR (400MHz, $CDCl_3$-10 % $DMSOd_6$): δ 8.0 (br, 3H), 3.8 (m, 1H), 3.65 (m, 1H), 3.55 (m, 1H), 3.47 (d, 1H), 3.35 (d, 1H), 0.9 (s, 3H), 0.85 (s, 3H). HRMS calcd. for $C_6H_{15}NO_2$ (M+H) : calcd. 134.1181, obs. 134.1178.

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12. We have never had any problems vacumn drying the reagent over P_2O_5 however, as with any azide, one should use caution. Excess azide has been used in solution with no loss in yield, and without concurrent isolation of intermediates **4** and **5**, however chromatographic purification of **3a** to remove $(n\text{-}Bu)_4N^+$ ^-OTf is necessary.

13. The main impurity is a 1:1 epimeric mixture of lactols which are easily separated from **8** by chromatography.

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